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|---|---|
| JIANG, SHAOJIA A | |
| **ART UNIT** | **PAPER NUMBER** |
| 1617 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/893,014 | FRIEDMAN ET AL. | |
| | Examiner | Art Unit | |
| | Shaojia A Jiang | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *3,4,7 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6 and 9-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/8/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 5, 2003 has been entered.

This Office Action is a response to Applicant's request for continued examination (RCE) filed July 30, 2003 in Paper No. 10, and response (remarks) to the Final Office Action (mailed June 3, 2003), filed December 5, 2003 wherein no claims have been amended.

Currently, claims 1-20 are pending in this application.

It is noted that Claims 3-4 and 7-8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected species, of record in the previous Office Action dated November 20, 2002. The claims have been examined insofar as they read on the elected specie, as indicated in the previous Office Action.

Claims 1-2, 5-6, and 9-11 are examined on the merits herein.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 and 9-11 are rejected under 35 U.S.C. 102(b) as being anticipated by CARPINO et al. (WO 98/58947, PTO-1449 submitted June 27, 2001).

The instant invention is drawn to employ the instant compounds of structural formula (I) alone or in combination of a growth hormone secretagogue selected from GHRP-6, GHRP-1, hexarelin and IGF-1, and IGF-II in a method for stimulating or increasing appetite in a patient.

CARPINO et al. discloses that the instant compounds of the structural formula (I) which covers the instant elected species, being growth hormone scretogogues, are useful in a pharmaceutical composition and methods for increasing levels of endogenous growth hormone and treating medical disorders associated to deficiency in growth hormone such as osteoporosis, frailty associated with aging, and obesity, in a human. CARPINO et al. also discloses the employment of the active compounds therein in combination of a growth hormone secretagogue selected from GHRP-6, GHRP-1, hexarelin and IGF-1, and IGF-II. See the abstract, page 1-28, page 52-59, and claims 77-106. CARPINO's method inherently stimulating or increasing appetite in a patient, as claimed herein since CARPINO's method steps are same as the instant method steps. Note that the amount of active compounds to be administered to a patient in instant invention is same as in CARPINO et al. See *Ex parte Novitski*, 26 USPQ 2d 1389. Moreover, the claiming of a new use, new function or unknown property which is inherently present in the prior art does not make the claim patentable. See *In re Best*,

562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also MPEP § 2112.01 with regard to inherency as it related to the claimed invention herein. Thus, CARPINO et al. anticipates claim 1 and 9-11.

Claims 1-2, 5-6 and 9-11 are rejected under 35 U.S.C. 102(b) as being anticipated by CARPINO et al. (WO 97/24369, PTO-1449 submitted June 27, 2001).

The instant invention is drawn to employ the instant compounds of structural formula (I) and (I-A) alone or in combination of a growth hormone secretagogue selected from GHRP-6, GHRP-1, hexarelin and IGF-1, and IGF-II in a method for stimulating or increasing appetite in a patient.

CARPINO et al. discloses that the instant compounds of the structural formula (I) which covers the instant elected species, which are growth hormone scretogogues, are useful in a pharmaceutical composition and methods for increasing levels of endogenous growth hormone and treating medical disorders associated to deficiency in growth hormone such as osteoporosis, frailty associated with aging, and obesity, in a human. See the abstract, page 1-2, page 4-11, page 17 lines 1-5, and claims 49-60. CARPINO et al. also discloses the employment of the active compounds therein in combination of a growth hormone secretagogue selected from GHRP-6, GHRP-1, hexarelin and IGF-1, and IGF-II. CARPINO's method inherently stimulating or increasing appetite in a patient, as claimed herein since CARPINO's method steps are same as the instant method steps. Note that the amount of active compounds to be administered in instant invention to a patient is same as in CARPINO et al. See *Ex parte*

*Novitski*, 26 USPQ 2d 1389. Moreover, the claiming of a new use, new function or unknown property which is inherently present in the prior art does not make the claim patentable. See *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also MPEP § 2112.01 with regard to inherency as it related to the claimed invention herein. Thus, CARPINO et al. anticipates claim 1-2, 5-6 and 9-11.

Applicant's remarks filed on December 5, 2003 with respect to these two rejections made under 35 U.S.C. 102(b) of record stated in the previous Office Action (June 3, 2003 have been fully considered but they are not deemed persuasive to render the claimed invention patentable over the prior art as further discussed below.

Applicant argues that WO 98/58947 or WO 97/24369 does not disclose or suggest the instant claimed method for stimulating or increasing appetite in a patient employing the instant compounds of structural formula (I) alone or in combination of a growth hormone secretagogue selected from GHRP-6, GHRP-1, hexarelin and IGF-1, and IGF-II. Moreover, Applicants' argument that increasing endogenous growth hormone levels with a compound of formula I does not necessarily result in the stimulation of appetite in a patient, have been considered but not found convincing.

It is the examiner's position that administering the same amount of the particular compound of CARPINO, being a growth hormone scretogogue, would inherently stimulate or increase appetite in a patient, or would necessarily result in the stimulation of appetite in a patient. The examiner's position is further supported by the teachings of Willesen et al. that "Stimulation of the actuate NPY neurons via GHS-R may explain the increased appetite and the cortisol release seen after administration of some GHS

compounds" ("GHS" represents Growth hormone secretagogues, see abstract of Willesen et al., PTO-892). The examiner's position is also supported by the teachings of Kaplowitz et al. "Cyproheptadine (Cp), an antihistamine serotonin antagonist drug with appetite-stimulating activity, was given to children with growth hormone (GH) deficiency to test the hypothesis that increased weight gain would enhance the effect of GH on linear growth" (see abstract of Kaplowitz et al.). Furthermore, as discussed in the previous Office Action, Vaccarino et al. discloses that a growth hormone secretagogue or a growth hormone-releasing factor is known to be useful in a method for treating appetite disorder in a patient or stimulating appetite in a patient.

Hence, the necessary consequence or certainty that a growth hormone secretagogue triggers appetite-stimulating activity (although the mechanism might not be well understood at some point) for the inherent treatment herein as one criteria for determining inherency is seen.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-16 even though they are not anticipated by CARPINO et al. reference (WO 98/5894 or WO 97/24369) as stated above in the 102(b) rejections, are rejected

under 35 U.S.C. 103(a) as being unpatentable over the same references by CARPINO et al. in view of Vaccarino et al. (CA 2095788, PTO-1449 submitted March 25, 2002) and The Merck Manual of Diagnosis and Therapy (16th ED) page 1529-1534.

Claims 12-16 are drawn to employ the instant compounds of structural formula (I) and (I-A) in combination of an antidepressant herein such as SSRI, MAO and atypical antidepressant, in a method for stimulating or increasing appetite in a patient.

CARPINO et al. discloses that the instant compounds of the structural formula (I) which covers the instant elected species, which are growth hormone scretogogues, are useful in a pharmaceutical composition and methods for increasing levels of endogenous growth hormone and treating medical disorders associated to deficiency in growth hormone such as osteoporosis, frailty associated with aging, and obesity, in a human. See the abstract, page 1-2, page 4-11, page 17 lines 1-5, and claims 49-60. CARPINO et al. also discloses the employment of the active compounds therein in combination of a growth hormone secretagogue selected from GHRP-6, GHRP-1, hexarelin and IGF-1, and IGF-II.

CARPINO et al. does not expressly disclose the employment of the instant compounds of structural formula (I) and (I-A) in combination of an antidepressant herein such as SSRI, MAO and atypical antidepressant, in a method for stimulating or increasing appetite in a patient.

Vaccarino et al. discloses that a growth hormone secretagogue or a growth hormone-releasing factor is known to be useful in a method for treating appetite disorder in a patient or stimulating appetite in a patient.

The Merck Manual of Diagnosis and Therapy (16th ED) teaches that an antidepressant herein such as SSRI, MAO and atypical antidepressant is known to be useful in the treatment of depression in a patient and decreasing appetite or anorexia is known to one of characteristic symptoms of depression. See page 1529-1534.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the instant compounds of structural formula (I) and (I-A) in combination of an antidepressant herein such as SSRI, MAO and atypical antidepressant, in a method for stimulating or increasing appetite in a patient.

One having ordinary skill in the art at the time the invention was made would have been motivated to the instant compounds of structural formula (I) and (I-A) in combination of an antidepressant herein such as SSRI, MAO and atypical antidepressant, in a method for stimulating or increasing appetite in a patient, since a growth hormone secretagogue or a growth hormone-releasing factor is known to be useful in a method for treating appetite disorder in a patient or stimulating appetite in a patient based on the prior art. Therefore, one of ordinary skill in the art would have reasonably expected that the instant compounds of the structural formula (I) formula (I) and (I-A) which are known growth hormone scretogogues, would be useful in method for treating appetite disorder in a patient or stimulating appetite in a patient. Moreover, an antidepressant herein such as SSRI, MAO and atypical antidepressant is well known to be useful in a method of the treatment of decreasing appetite or anorexia, a known characteristic symptom of depression in a patient according to The Merck Manual of Diagnosis and Therapy (16th ED). Therefore, one of ordinary skill in the art would have

reasonably expected that combining the instant compounds of structural formula (I) and (I-A) in combination of an antidepressant herein known to be useful individually for the same purpose, i.e., stimulating or increasing appetite in a patient, in a pharmaceutical composition to be administered would improve the therapeutic effect for stimulating or increasing appetite.

Since all active composition components herein are known to useful to stimulate or increase appetite, it is considered prima facie obvious to combine them into a single composition to form a third composition useful for the very same purpose. At least additive therapeutic effects would have been reasonably expected. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Claims 17-20 even though they are not anticipated by CARPINO et al. reference (WO 98/5894 or WO 97/24369) as stated above in the 102(b) rejections, are rejected under 35 U.S.C. 103(a) as being unpatentable over the same references by CARPINO et al. in view of Vaccarino et al. (CA 2095788, PTO-1449 submitted March 25, 2002) and The Merck Manual of Diagnosis and Therapy (16$^{th}$ ED) page 1529-1534, and The Pharmacological Basis of Therapeutics (1996) page 928-932 and 339-430 (see also the specification regarding prior art at 36-37).

Claims 17-20 are drawn to employ the instant compounds of structural formula (I) and (I-A) in combination of an antiemetic herein or antipsychotic, in a method for stimulating or increasing appetite in a patient.

CARPINO et al. discloses that the instant compounds of the structural formula (I) which covers the instant elected species, which are growth hormone scretogogues, are useful in a pharmaceutical composition and methods for increasing levels of endogenous growth hormone and treating medical disorders associated to deficiency in growth hormone such as osteoporosis, frailty associated with aging, and obesity, in a human. See the abstract, page 1-2, page 4-11, page 17 lines 1-5, and claims 49-60. CARPINO et al. also discloses the employment of the active compounds therein in combination of a growth hormone secretagogue selected from GHRP-6, GHRP-1, hexarelin and IGF-1, and IGF-II.

CARPINO et al. does not expressly disclose the employment of the instant compounds of structural formula (I) and (I-A) in combination of an antiemetic herein or antipsychotic, in a method for stimulating or increasing appetite in a patient.

Vaccarino et al. discloses that a growth hormone secretagogue or a growth hormone-releasing factor is known to be useful in a method for treating appetite disorder in a patient or stimulating appetite in a patient.

An antiemetic herein or antipsychotic is known to be useful in treating decreasing appetite or anorexia in depression according to The Merck Manual of Diagnosis and Therapy (16$^{th}$ ED) and The Pharmacological Basis of Therapeutics (1996) page 928-932 and 339-430 (see also the specification regarding prior art at page 36-37).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the instant compounds of structural formula (I) and (I-A)

in combination of an antiemetic herein or antipsychotic herein, in a method for stimulating or increasing appetite in a patient.

One having ordinary skill in the art at the time the invention was made would have been motivated to the instant compounds of structural formula (I) and (I-A) in combination of an antidepressant herein such as SSRI, MAO and atypical antidepressant, in a method for stimulating or increasing appetite in a patient, since a growth hormone secretagogue or a growth hormone-releasing factor is known to be useful in a method for treating appetite disorder in a patient or stimulating appetite in a patient based on the prior art. Therefore, one of ordinary skill in the art would have reasonably expected that the instant compounds of the structural formula (I) formula (I) and (I-A) which are known growth hormone scretogogues, would be useful in method for treating appetite disorder in a patient or stimulating appetite in a patient. Moreover, an antiemetic herein or antipsychotic herein is well known to be useful in a method of the treatment of decreasing appetite or anorexia, a known characteristic symptom of depression in a patient according to The Merck Manual of Diagnosis and Therapy ($16^{th}$ ED) and The Pharmacological Basis of Therapeutics (1996) page 928-932 and 339-430. Therefore, one of ordinary skill in the art would have reasonably expected that combining the instant compounds of structural formula (I) and (I-A) in combination of an antiemetic herein or antipsychotic herein known to be useful individually for the same purpose, i.e., stimulating or increasing appetite in a patient, in a pharmaceutical composition to be administered would improve the therapeutic effect for stimulating or increasing appetite.

Since all active composition components herein are known to useful to stimulate or increase appetite, it is considered prima facie obvious to combine them into a single composition to form a third composition useful for the very same purpose. At least additive therapeutic effects would have been reasonably expected. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Applicant's remarks filed on December 5, with respect to these rejections made under 35 U.S.C. 103(a) of record in the previous Office Action have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art.

Applicant's argument regarding that Carpino et al. references do not teach or suggest the claimed method herein has been discussed above in the 102(b) rejections. Applicant's argument that Vaccarino et al. does not teach any other growth hormone secretagogue, is not found convincing. Carpino et al. has been cited by the examiner primarily for its teachings that a growth hormone secretagogue or a growth hormone-releasing factor is known to be useful in a method for treating appetite disorder in a patient or stimulating appetite in a patient, which supports the examiner's position in the inherency issue above.

Applicant also asserts that the Merck Manual at page 1533 teaches away from the instant combination in the claimed method. However, the Merck Manual at page

1533 teaches that anorexia, the adverse effect by SSRIs, can occur merely in the first few months, especially with fluoxetine. It is noted that the instant claims are not limited to the particular antidepressants, SSRIs such as fluoxetine. Moreover, a typical antidepressant is known to be useful in the treatment of depression in a patient suffering from decreasing appetite or anorexia, which is known to one of characteristic symptoms of depression (see the Merck Manual page 1529-1534).

Applicant further argues no motivation to combine the compound herein and an antidepressant. As discussed in the previous Office Action, one of ordinary skill in the art would have reasonably expected that combining the instant compounds of structural formula (I) and (I-A) in combination of an antidepressant herein known to be useful individually for the same purpose, i.e., stimulating or increasing appetite in a patient, in a pharmaceutical composition to be administered would improve the therapeutic effect for stimulating or increasing appetite. It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form a third composition that is to be used for the very same purpose; idea of combining them flows logically from their having been individually taught in prior art. *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

Therefore, motivation to combine the teachings of the prior art cited herein to make the present invention is seen. The claimed invention is clearly obvious in view of the prior art.

Further, the record contains no clear and convincing evidence of nonobviousness or unexpected results for the combinations in the claimed method herein over the prior art. It is also noted that no testing data in the record show that the instant compound increases or stimulates appetite in *vivo* or useful in the instant claimed method of treatment. In this regard, it is noted that the specification provides no side-by-side comparison with the closest prior art in support of nonobviousness for the instant claimed invention over the prior art.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is 571.272.0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on 571.272.0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.

S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
March 4, 2004